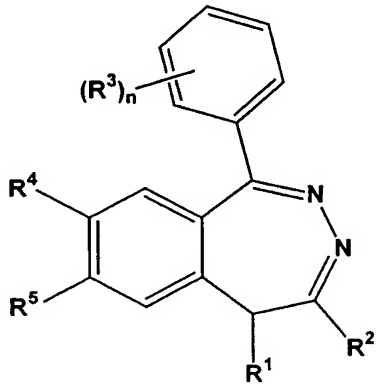
CLAIMS

What is claimed is:

1. A method of treating an individual afflicted with an inflammatory disorder comprising administering to said individual an effective amount of at least one compound according to Formula I:



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wherein:

R^1 is -(C_1-C_7)hydrocarbyl or -(C_2-C_6)heteroalkyl;

R^2 is selected from the group consisting of –H, and -(C_1-C_7)hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, -O-acyl, -SH, –S(C_1-C_3)alkyl, –NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NH-acyl, -NO_2 and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, O-acyl, -SH, –S(C_1-C_3)alkyl, –NH_2, NH-acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5-, 6- or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

2. The method according to claim 1, wherein said inflammatory disorders are mediated by LTB_4.

3. The method according to claim 1 wherein the compound according to formula I comprises a racemic mixture of (*R*)- and (*S*)- enantiomers with respect to the absolute conformation at the 5-position of the benzodiazepine ring.

4. The method according to claim 3, wherein:

R^1 is -(C_1-C_6)alkyl;

R^2 is selected from the group consisting of –H and -(C_1-C_6)alkyl;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -O-acyl and -OH;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -O-acyl and -OH, wherein, R^4 and R^5 may combine to form a 5-, 6- or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

5. The method according to claim 4, wherein:

R^1 is $–CH_2CH_3$;

R^2 is $–CH_3$

R^3, R^4 and R^5 are independently selected from the group consisting of –OH and –O(C_1-C_6)alkyl;

n is 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

6. The method according to claim 5, wherein:

R^1 is $–CH_2CH_3$;

R^2 is $–CH_3$

R^3, R^4 and R^5 are independently selected from the group consisting of –OH and $–OCH_3$;

n is of 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

7. The method according to claim 6, wherein the compound is selected from the group consisting of:

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine;

1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

and pharmaceutically acceptable salts thereof.

8. The method according to claim 7, wherein the compound is 1-(3,4-dimethoxy-phenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine; or

a pharmaceutically acceptable salt thereof.

9. The method according to claim 1, wherein said wherein said compounds according to formula I are (*R*)-enantiomers substantially free of the corresponding (*S*)-enantiomers, with respect to the absolute conformation at the 5-position of the benzodiazepine ring.

10. The method according to claim 9, wherein:

R^1 is -(C_1-C_6)alkyl;

R^2 is selected from the group consisting of –H and -(C_1-C_6)alkyl;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -O-acyl and -OH;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -O-acyl and -OH, wherein, R^4 and R^5 may combine to form a 5-, 6- or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

11. The method according to claim 10, wherein:

R^1 is $–CH_2CH_3$;

R^2 is $–CH_3$

R^3, R^4 and R^5 are independently selected from the group consisting of –OH and –O(C_1-C_6)alkyl;

n is 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

12. The method according to claim 11, wherein:

R^1 is $–CH_2CH_3$;

R^2 is $–CH_3$

R^3, R^4 and R^5 are independently selected from the group consisting of –OH and $–OCH_3$;

n is of 1, 2 or 3;

or a pharmaceutically-acceptable salt of such a compound.

13. The method according to claim 12, wherein the compound is selected from the group consisting of:

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3,4-dimethoxyphenyl)-4-methyl-5-ethyl-7-methoxy-8-hydroxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-methoxy-4-hydroxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

(*R*)-1-(3-hydroxy-4-methoxyphenyl)-4-methyl-5-ethyl-7-hydroxy-8-methoxy-5H-2,3-benzodiazepine;

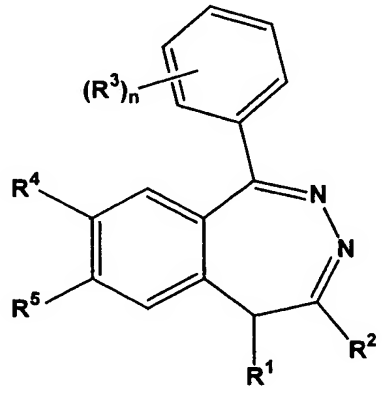
substantially free of the corresponding (*S*)-enantiomers;

and pharmaceutically acceptable salts thereof.

14. The method according to claim 13, wherein the compound is (*R*)-1-(3,4-dimethoxy-phenyl)-4-methyl-5-ethyl-7,8-dimethoxy-5H-2,3-benzodiazepine substantially free of the corresponding (*S*)-enantiomer;

or a pharmaceutically acceptable salt thereof.

15. A method of treating an individual afflicted with an inflammatory disorder comprising administering to said individual an effective amount of a combination of at least one compound according to Formula I:



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wherein:

R^1 is -(C_1-C_7)hydrocarbyl or -(C_2-C_6)heteroalkyl;

R^2 is selected from the group consisting of –H, and -(C_1-C_7)hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, -O-acyl, -SH, –S(C_1-C_3)alkyl, –NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NH-acyl, -NO_2 and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, O-acyl, -SH, –S(C_1-C_3)alkyl, –NH_2, NH-acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5-, 6- or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound; and

one or more additional therapeutic agents selected from the group consisting of aminosalicylates, corticosteroids, antimetabolites, immunosuppressants, tumor necrosis factor alpha inhibitors, inhibitors of leukotriene synthesis, and leukotriene antagonists;

wherein the additional therapeutic agents that are leukotriene antagonists are other than compounds of formula I.

16. The method according to claim 15, wherein the amino salicylate is selected from the group consisting of sulfasalazine and mesalamine.

17. The method according to claim 15, wherein the corticosteroid is selected from the group consisting of prednisone and budesonide.

18. The method according to claim 15, wherein the antimetabolite is azathioprine.

19. The method according to claim 15, wherein the immunosuppressant is selected from the group consisting of cyclosporine and tacrolimus.

20. The method according to claim 15, wherein the tumor necrosis factor alpha inhibitor is selected from the group consisting of infliximab, etanercept, and adalimumab.

21. The method according to claim 15, wherein the inhibitor of leukotriene synthesis is a 5-lipoxygenase inhibitor.

22. The method according to claim 21, wherein the 5-lipoxygenase inhibitor is selected from the group consisting of ETH615, linetastine, lonapalene, MK 886, and zileuton.

23. The method according to claim 15, wherein the inhibitor of leukotriene synthesis is selected from the group consisting of 15-HETE and leflunomide.

24. The method according to claim 15, wherein the leukotriene antagonist is selected from the group consisting of SC41930, SC53228, CGS-25019C, ONO-4057, SB-202247, VML295, CP-105696, CP-195543, and U-75302.

25. The method according to claim 1 wherein the inflammatory disorder is inflammatory bowel disease.

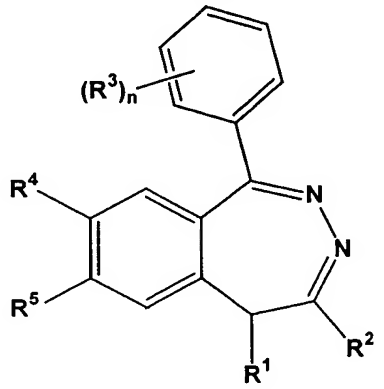
26. The method according to claim 25 wherein the inflammatory bowel disease occurs in an individual suffering from irritable bowel syndrome.

27. The method according to claim 2 wherein the inflammatory disorder is selected from the group consisting of psoriasis, rheumatoid arthritis, and radiation–induced gastrointestinal inflammation.

28. The method according to claim 27 wherein the inflammatory disorder occurs in an individual suffering from irritable bowel syndrome.

29. A method of preventing or delaying the onset of an inflammatory disorder in an individual who is at risk of developing an inflammatory disease state, said method comprising:

administering to said individual an effective amount of at least one compound according to formula I as described in claim 1:



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wherein:

R^1 is -(C_1-C_7)hydrocarbyl or -(C_2-C_6)heteroalkyl;

R^2 is selected from the group consisting of –H, and -(C_1-C_7)hydrocarbyl;

wherein R^1 and R^2 may combine to form a carbocyclic or heterocyclic 5- or 6-membered ring;

R^3 is independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, -O-acyl, -SH, –S(C_1-C_3)alkyl, –NH_2, -NH(C_1-C_6)alkyl, -N((C_1-C_6)alkyl)$_2$, -NH-acyl, -NO_2 and halogen;

n is 1, 2 or 3;

R^4 and R^5 are independently selected from the group consisting of –O(C_1-C_6)alkyl, -OH, O-acyl, -SH, –S(C_1-C_3)alkyl, –NH_2, NH-acyl and halogen;

wherein, R^4 and R^5 may combine to form a 5, 6 or 7-membered heterocyclic ring;

or a pharmaceutically-acceptable salt of such a compound.

30. The method according to claim 29 wherein the inflammatory disorder is mediated by LTB_4.

31. The method according to claim 29, wherein said wherein said compounds according to formula I are (*R*)-enantiomers substantially free of the corresponding (*S*)-enantiomers, with respect to the absolute conformation at the 5-position of the benzodiazepine ring.